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Dedicated to Professor Paul Messinger on the occasion of his 60th birthday

The synthesis of some derivatives of the novel heterocyclic ring system pyrido[3,4-*d*][1]benzazepine is reported. Thus, pyrido[3,4-*d*][1]benzazepin-7-one **6** was prepared by cyclisation of the Michael adduct **5** with ammonium ferric sulfate. Reaction of **6** with phosphorus pentasulfide gave the thiolactam **7**, which after methylation and subsequent reaction with amines furnished the amidines **10**.

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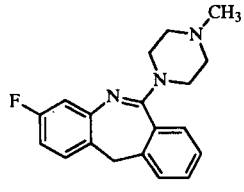
The class of *c*-fused 1-benzazepines has been extensively investigated synthetically and pharmacologically. Several of these compounds exhibit biological properties, namely on the central nervous system. One prominent example in this series is fluperlapine **1**, which was studied clinically as nonclassical antipsychotic [2]. In contrast, only a few tricyclic *d*-fused 1-benzazepines are known, for instance pyrazolo-, isoxazolo-, thiadiazolo-, and cyclopentano-condensed derivatives [3,4]. The pyrimido[5,4-*d*][1]benzazepine **2** has been shown to be a competitive inhibitor of diazepam in the ^{3}H-benzodiazepine receptor binding assay [5].



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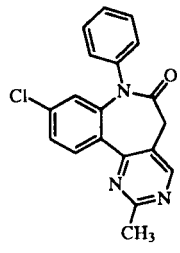

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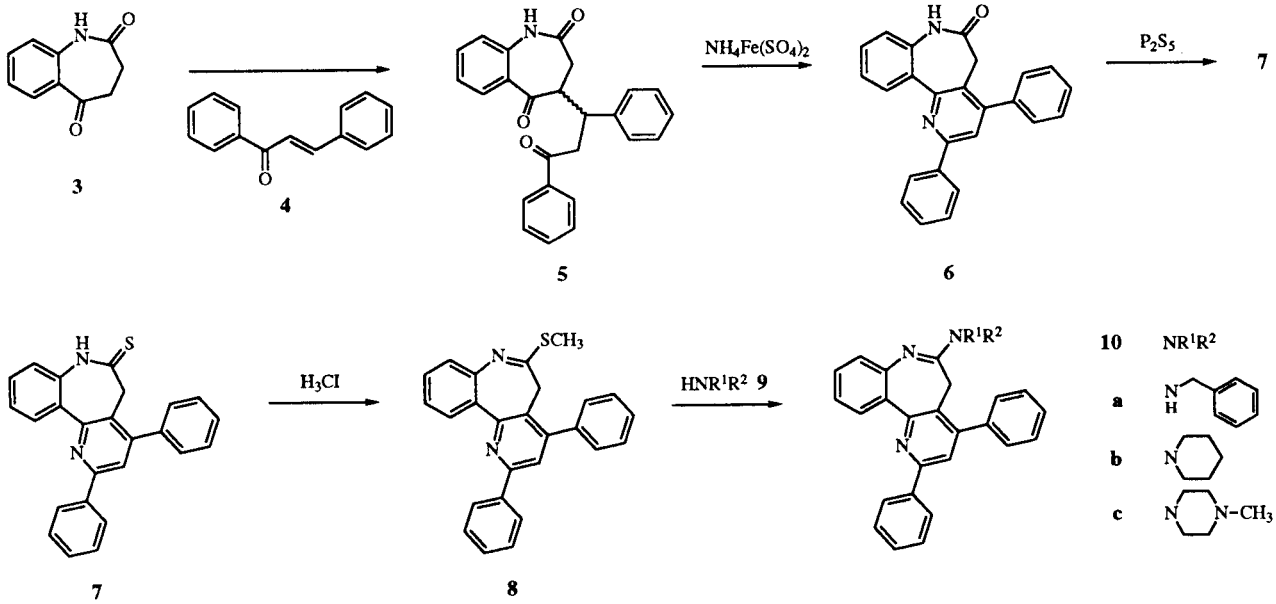
In the course of our studies on novel *d*-fused 1-benzazepines it was intended to prepare pyrido[3,2-*d*][1]benzazepines including an amidine moiety, aiming to find centrally acting compounds.

The synthetic route to the novel ring system is outlined in the reaction scheme. The 1*H*-1-benzazepine-2,5(3*H*,4*H*)-dione **3**, which was used as starting material, was prepared according to a method described recently [6]. Michael reaction of **3** with benzylideneacetophenone **4** in ethanolic potassium hydroxide solution at room temperature afforded the addition product **5** as an approximate 1:1 mixture of diastereomers, which were not separated. The attempted ring closure of **5** using hydroxylamine hydrochloride in ethanol gave only poor yields of the desired product **6** together with a number of unidentified by-products. On the contrary, when **5** was refluxed



with ammonium ferric sulfate in glacial acetic acid cyclization occured to yield the pyrido[3,2-*d*][1]benzazepinone **6**. The lactam **6** was converted subsequently to the thiolactam **7** by means of phosphorus pentasulfide and sodium bicarbonate in tetrahydrofuran. Methylation of **7** by treatment with sodium hydride and iodomethane in tetrahydrofuran furnished the thiolactim ether **8**. When **8** was heated with aliphatic primary or secondary amines **9**, the semicyclic amidines **10a-c** were obtained.

The conformational flexibilities of the described pyrido[3,4-*d*][1]benzazepines depend on the nature of the bonds between positions 6 and 7 of the ring system and decrease in the series **6 > 7/9/10a > 10b/10c**. This may be concluded from the pmr spectra of the compounds, where the shape of the azepine methylene signal indicates the azepine flexibility [7]. When the ring flipping is rapid in terms of the pmr time scale, a singlet appears, because the methylene protons become magnetically equivalent. This is the case in the lactam **6**, where a broad methylene singlet is observed. Low frequency of ring inversion gives a splitting of the signal, because a pseudo-axial and a pseudo-equatorial methylene proton can be distinguished. Hence, in the spectra of the compounds **7**, **8** and **10a** the signal is split into two broad peaks, due to a higher energetic barrier for the rotation of the 6-7 bond. In the amidines **10b** and **10c** the methylene protons of the azepine ring cause AB-systems. The higher rigidity in these compounds may refer to the additional steric hindrance by the cyclic amino substituents compared to the *N*-benzyl substituent in **10a**.

EXPERIMENTAL

Melting points were determined on an electric variable heater (Gallenkamp) and evaluated on a Mettler FP 62 automatic melting point instrument. Elemental analyses were performed on a Heraeus CHN-O-Rapid apparatus. Infrared spectra were recorded on a Pye Unicam SP1100 or a Pye Unicam SP3-200S spectrophotometer, respectively. Nuclear magnetic resonance spectra were recorded on a Bruker AC 250P or a Bruker AMX 400 instrument, respectively, using tetramethylsilane as internal standard. The ^{13}C nmr spectra were recorded as ^{1}H-decoupled spectra and DEPT spectra. Solvents were purified according to published methods [8]. Thus, tetrahydrofuran was passed through a column of basic alumina and then distilled from potassium hydroxide. Ethanol was refluxed with sodium and subsequently with diethyl phthalate and then distilled.

(±)4-(3-Oxo-1,3-diphenyl-propyl)1*H*-1-benzazepin-2,5(3*H*,4*H*)-dione, Mixture of Diastereomers **5**.

A suspension of 1.75 g (10 mmoles) 1*H*-1-benzazepin-2,5(3*H*,4*H*)-dione (**3**) [6], 2.08 g (10 mmoles) benzylideneacetophenone (**4**) and 56 mg (1 mmole) potassium hydroxide in 35 ml of ethanol was stirred at room temperature for 5 hours. Acetic acid was added dropwise until the mixture became slightly acidic (*p*H 5). The resulting precipitate was filtered, washed with cold ethanol and water and crystallized from ethanol to yield 2.98 g (78%) as colorless crystals, mp 195-202°; ir (potassium bromide): 3210 (NH) 1670 cm^{-1} (C=O); ^{1}H nmr (400 MHz; dimethyl sulfoxide-d_6): δ 2.41 (dd, 0.5H, J = 11.2, 14.8 Hz, aliphatic H), 2.64 (dd, 1H, J = 7.4, 14.8 Hz, aliphatic H), 2.98 (dd, 0.5H, J = 11.2, 14.8 Hz, aliphatic H), 3.21-3.30 (m, 1.5H, overlapping the water signal, aliphatic H), 3.50-3.60 (m, 1H, aliphatic H), 3.82 (dd, 0.5H, J = 10.4, 17.6 Hz, aliphatic H), 4.0 (q, 0.5H, J = 7.6 Hz, aliphatic H), 4.12 (m, 0.5 H, aliphatic H), 7.08-7.31 (m, 7H, aromatic H), 7.45-7.55 (m, 3H, aromatic H), 7.57-7.75 (m, 2H, aromatic H), 7.85-8.0 (m, 2H, aromatic H), 10.16 (s, 0.5H, NH), 10.22 (s, 0.5H, NH).

Anal. Calcd. for $C_{25}H_{21}NO_3$: C, 78.31; H, 5.52; N, 3.65. Found: C, 78.06; H, 5.62; N, 4.02.

2,4-Diphenyl-5*H*-pyrido[3,2-*d*][1]benzazepin-6(7*H*)-one (**6**).

A mixture of 10.1 g (26.4 mmoles) of **5**, 27 g (56 mmoles) of ammonium ferric sulfate dodecahydrate and 31 g (402 mmoles) of ammonium acetate in 198 ml of glacial acetic acid was refluxed under nitrogen for 3 hours. The reaction mixture was poured onto 200 g of ice. A grey solid separated, which was filtered, washed with water and crystallized from ethanol/toluene to give 5.65 g (58%) transparent brown needles. After repeated recrystallization from ethanol/toluene, an analytical sample was obtained as colorless crystals, mp 252°; ir (potassium bromide): 3180 (NH), 1670 cm^{-1} (C=O); ^{1}H nmr (400 MHz; dimethyl sulfoxide-d_6): δ 3.4 (br s, 2H, CH_2), 7.26 (d, 1H, J = 8 Hz, aromatic H), 7.37 (t, 1H, J = 7.4 Hz), 7.44-7.56 (m, 6H, aromatic H), 7.6 (t, 1H, J = 7.4 Hz, aromatic H), 7.64-7.7 (m, 2H, aromatic H), 7.96 (s, 1H, pyridine H), 8.19-8.28 (m, 3H, aromatic H), 10.4 (s, 1H, NH); ^{13}C nmr (100.62 MHz, dimethyl sulfoxide-d_6): δ 35.4 (CH_2), 120.2, 121.4, 123.8, 126.8, 128.4, 128.5, 128.7, 129.1, 129.6, 129.8, 131.1 (aromatic tertiary C), 125.4, 131.0, 137.4, 137.7, 138.2, 149.3, 154.1, 154.5 (aromatic quarternary C), 171.1 (C=O).

Anal. Calcd. for $C_{25}H_{18}N_2O$: C, 82.85; H, 5.01; N, 7.73. Found: C, 82.74, H, 5.11; N, 7.82.

2,4-Diphenyl-5*H*-pyrido[3,2-*d*][1]benzazepin-6(7*H*)-thione (**7**).

To a solution of 5.2 g (14.3 mmoles) of **6** in 300 ml of tetrahydrofuran, which was stirred under nitrogen at 50°, 5.6 g phosphorus pentasulfide was added. After 30 seconds, 8.2 g (97 mmoles) of sodium bicarbonate was added. The mixture was refluxed for 3 hours, allowed to cool to room temperature and then poured into 400 ml of ice water. The precipitate was filtered and crystallized from ethanol/toluene to give 4.22 g (78%) colorless crystals, mp 286° dec; ir (potassium bromide): 3160 cm^{-1} (NH); ^{1}H nmr (400 MHz; dimethyl sulfoxide-d_6): δ 3.55 (br "s", 1H, CH_2), 4.2 (br "s", 1H, CH_2), 7.2-7.9 (m, 11H, aromatic H), 7.95 (s, 1H, pyridine H), 8.2-8.3 (m, 3H, aromatic H), 12.38 (s, 1H, NH); ^{13}C nmr (100.62 MHz, dimethyl sulfoxide-d_6): δ 42.8 (CH_2), 120.9, 121.8, 125.5, 126.8, 128.2, 128.3, 128.7, 129.2, 129.7, 129.8, 131.2 (aromatic tertiary carbons), 127.1, 132.2, 137.5, 138.0, 149.6, 153.3, 154.9 (aromatic quarternary carbons, at 137.5 two signals overlapping), 200.6 (C=S).

Anal. Calcd. for $C_{25}H_{18}N_2S$: C, 79.33; H, 4.79; N, 7.40; S, 8.47. Found: C, 79.16; H, 4.90; N, 7.50; S, 8.31.

6-Methylthio-2,4-diphenyl-5*H*-pyrido[3,2-*d*][1]benzazepine (**8**).

To a solution of 4.0 g (10.57 mmoles) of **7** in 200 ml tetrahydrofuran 0.423 g (10.58 mmoles) of a sodium hydride dispersion

(60%, in mineral oil) was added. The mixture was refluxed for 45 minutes and cooled to room temperature. A solution of 1.74 g (12.26 mmoles) iodomethane in 2 ml of tetrahydrofuran was added and the mixture was refluxed for an additional 90 minutes. The solution was then allowed to cool to room temperature and was poured into 300 ml of ice water. A yellowish solid precipitated, which was collected and recrystallized from ethanol/toluene to give 3.8 g (92%) colorless crystals, mp 194.5°; ir (potassium bromide): 3060, 1590 cm^{-1}; ^1H nmr (400 MHz, deuteriochloroform): δ 2.42 (s, 3H, CH_3), 3.05 (br "s", 1H, CH_2), 3.7 (br "s", 1H, CH_2), 7.25-7.58 (m, 11H, aromatic H), 7.69 (s, 1H, pyridine H), 8.12-8.4 (m, 3H, aromatic H); ^{13}C nmr (100.62 MHz, deuteriochloroform): δ 13.5 (CH_3), 35.5 (CH_2), 120.5, 124.1, 126.3, 127.0, 128.2, 128.5, 128.7, 129.0, 129.2, 131.2 (aromatic tertiary carbons, one signal missing due to peak overlapping), 131.1, 138.6, 139.1, 146.8, 149.3, 154.4, 155.3 (aromatic quarternary carbons, one signal missing due to peak overlapping), 164.6 (C-6).

Anal. Calcd. for $C_{26}H_{20}N_2S$: C, 79.56; H, 5.14; N, 7.14; S, 8.17. Found: C, 79.76; H, 5.32; N, 7.32; S, 8.27.

6-Benzylamino-2,4-diphenyl-5*H*-pyrido[3,2-*d*][1]benzazepine (**10a**).

A mixture of 0.2 g (0.51 mmoles) of **8** and 1.1 g (10.27 mmoles) of freshly distilled benzylamine was refluxed in 20 ml of xylene for 40 hours. After evaporation *in vacuo*, the red oily residue solidified upon standing. The solid was collected and recrystallized from ethanol and subsequently from toluene/petroleum benzin (bp 40-60°) to yield 126 mg (55%) of colorless crystals, mp 189°; ir (potassium bromide): 3280 cm^{-1} (NH); ^1H nmr (250 MHz, dimethyl sulfoxide-d_6): δ 2.96 (br "s", 1H, azepine CH_2), 3.70 (br "s", 1H, azepine CH_2), 4.42 (br s, 2H, benzyl CH_2), 7.00-7.65 (m, 17H, NH and aromatic H), 7.82 (s, 1H, pyridine H), 8.09-8.28 (m, 3H, aromatic H); ^{13}C nmr (100.62 MHz, dimethyl sulfoxide-d_6): δ 31.8 (CH_2), 44.2 (CH_2), 119.7, 120.7, 126.1, 126.5, 126.6, 127.3, 127.9, 128.0, 128.6, 128.9, 129.0, 130.7 (aromatic tertiary carbons, two signals missing due to peak overlapping), 127.1, 130.5, 138.3, 138.4, 139.6, 148.1, 148.7, 153.7, 154.7 (aromatic quarternary carbons and C-6, one signal missing due to peak overlapping).

Anal. Calcd. for $C_{32}H_{25}N_3$: C, 85.11; H, 5.58; N, 9.31. Found: C, 84.81; H, 5.89; N, 9.59.

6-Piperidino-2,4-diphenyl-5*H*-pyrido[3,2-*d*][1]benzazepine (**10b**).

A solution of 0.1 g (0.26 mmoles) of **8** in 3 ml (30.33 mmoles) of freshly distilled piperidine was refluxed for 36 hours. The solution was allowed to cool to room temperature and was then poured into 20 ml of ice water. After stirring the mixture for 15 minutes, the precipitate was filtered, washed with water and recrystallized from ethanol to yield 62 mg (57%) colorless needles, mp 234°; ir (potassium bromide): 2930 (C-H), 1580 cm^{-1}; ^1H nmr (250 MHz, dimethyl sulfoxide-d_6): δ 1.10-1.55 (m, 6H, piperidine CH_2), 2.67 (d, 1H, J = 13.6 Hz, azepine CH_2), 2.8-3.2 (m, 4H, piperidine CH_2), 4.25 (d, 1H, J = 13.6 Hz, azepine CH_2), 7.05-7.20 (m, 2H, aromatic H), 7.35-7.67 (m, 9H, aromatic H), 7.88 (s, 1H, pyridine H), 8.16 (dd, 1H, J = 1.6, 7.8 Hz, aromatic H), 8.22 (d, 2H, J = 6.6 Hz, aromatic H). Due to poor solubility of **10b**, a ^{13}C nmr spectrum was not recorded.

Anal. Calcd. for $C_{30}H_{27}N_3$: C, 83.88; H, 6.34; N, 9.78. Found: C, 84.09; H, 6.60; N, 10.10.

6-(4-Methyl-1-piperazinyl)-2,4-diphenyl-5*H*-pyrido[3,2-*d*]-[1]benzazepine (**10c**).

A solution of 0.1 g (0.26 mmoles) of **8** in 3 ml (27.04 mmoles) of freshly distilled *N*-methylpiperazine was refluxed for 36 hours. The solution was allowed to cool to room temperature and was then poured into 20 ml of ice water. After stirring the mixture for 15 minutes, the precipitate was filtered, washed with water and recrystallized from ethanol to yield 60 mg (52%) of colorless crystals, mp 250°; ir (potassium bromide): 2930 (C-H), 1580 cm^{-1}; ^1H nmr (250 MHz; dimethyl sulfoxide-d_6): δ 2.04 (br s, 4H, piperazine CH_2, overlapping the following signal), 2.09 (s, 3H, CH_3), 2.67 (d, 1H, J = 13.6 Hz, azepine CH_2), 2.8-3.2 (m, 4H, piperazine CH_2), 4.21 (d, 1H, J = 13.6 Hz, azepine CH_2), 7.05-7.20 (m, 2H, aromatic H), 7.35-7.65 (m, 9H, aromatic H), 7.89 (s, 1H, pyridine H), 8.18 (dd, 1H, J = 1.6, 8.0 Hz, aromatic H), 8.22 (dd, 2H, J = 8.0, 1.6 Hz, aromatic H). Due to poor solubility of **10c**, a ^{13}C nmr spectrum was not recorded.

Anal. Calcd. for $C_{30}H_{28}N_4$: C, 81.05; H, 6.35; N, 12.60. Found: C, 80.71; H, 6.67; N, 12.49.

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REFERENCES AND NOTES

[1] Presented in part at the Second European Congress of Pharmaceutical Sciences, Berlin, Germany, 1994.

[2a] E. Eichenberger, *Arzneim. Forsch,* **34**, 110 (1984); [b] B. Woggon, K. Heinrich, B. Küfferle, B. Müller-Oerlinghausen, W. Pöldinger, E. Rüther and H. W. Schied, *Arzneim. Forsch.*, **34**, 122 (1984); [c] K. A. Fischer-Cornelssen, *Arzneim. Forsch.*, **34**, 125 (1984).

[3] G. R. Proctor and B. M. L. Smith, *J. Chem. Soc., Perkin Trans. 1,* 862 (1978).

[4] A. Bertho, *Chem. Ber.*, **90**, 29 (1957).

[5] W.-Y. Chen and N. W. Gilman, *J. Heterocyclic Chem.*, **20**, 663 (1983).

[6] C. Kunick, *Arch. Pharm. (Weinheim),* **324**, 579 (1991).

[7a] W. Tochtermann, *Fortschr. Chem. Forsch.*, **15**, 378 (1970); [b] A. Mannschreck, G. Rissmann, F. Vögtle and D. Wild, *Chem. Ber.*, **100**, 335 (1967); [c] C. Kunick, *Liebigs Ann. Chem.*, 1141 (1993).

[8] D. D. Perrin and W. L. F. Armarego, Purification of Laboratory Chemicals, 3rd ed, Pergamon Press, Oxford, England, 1988.